REMARKS

Applicant's attorney wishes to thank the Examiner for the careful consideration given to the present application and the courteous interview extended to Ray Miller and the undersigned on September 23, 2008. Currently, claims 1-6 are canceled, claims 7-8, 13-20 and 25-30 have been amended and new claims 31-40 have been added. Support for new claims 31-40 may be found at, for example, paragraph [0215] of the specification, as discussed in more detail below. Accordingly, claims 7-40 are pending. Applicant addresses each of the rejections set forth in the Office Action in the order presented therein.

Related Applications

Applicant would like to again remind the Examiner of the related, co-pending Application No. 10/366,751 filed on February 14, 2003, which is presenting related claims (i.e. composition comprised of a pharmacologically effective amount of 1-methylpropyl-2-imidazolyl disulfide and a pharmaceutically acceptable carrier), which are currently under appeal.

35 U.S.C. § 102(b)

The Examiner has rejected claims 7-30 under 35 U.S.C. § 102(b) as being anticipated by Oblong et al. as evidenced by Chaplan et al., (U.S. Patent No. 5,849,737) and Padmanaban (U.S. Application No. 200701059455). Applicant respectfully disagrees

A review of literature demonstrates that one of ordinary skill in the art would not understand that DMSO could be considered a suitable carrier for injection or oral administration, as evidenced by The Merck Index, Material Safety Data Sheet and several peer reviewed journals (attached as **Exhibit A**), which teach that exposure to DMSO causes adverse effects in human subjects and thus DMSO is not considered a "pharmaceutically acceptable carrier".

Even assuming arguendo that the Examiner has established that DMSO is a suitable carrier for injection and oral formulation, Oblong fails to disclose a drug comprising a 2-imidazolyl disulfide and a pharmaceutically acceptable carrier for either injection or oral administration that is formulated in a suitable dosage amount for reducing or eliminating thioredoxin-associated apoptosis inhibition or thioredoxin stimulated cell growth as set forth in pending claims 7-40. Further there is no correlation between the *in vitro* dosage amount of 2-imidazolyl disulfide in DMSO (a great organic solvent) and achieving a suitable dosage amount of 2-imidazolyl disulfide in other pharmaceutically acceptable carriers. Oblong fails to teach or

even suggest specific appropriate *in vivo* dosages of 1-methylpropyl-2-imidazolyl disulfide and discloses only *in vitro* dosages of 1-methylpropyl-2-imidazolyl disulfide. Claims 7-30 recite that the 2-imidazolyl disulfide is formulated in a suitable dosage amount for reducing or eliminating thioredoxin-associated apoptosis inhibition or inhibiting thioredoxin stimulated cell growth and new claims 31-40 are directed to specific dosages of 1-methylpropyl-2-imidazolyl disulfide for injection and oral administration. As set forth in the specification in paragraph [0215], Applicant teaches that when *min*-positive mice are fed a diet of 250 ppm of 1-methylpropyl-2-imidazolyl disulfide, the number of tumors in the colon are reduced by 70%, and a significant reduction in the size of remaining tumors occurs. It is known to one of ordinary skill in the art that a dose of one ppm (parts per million) is equivalent to one mg/kg. Therefore, based on the above references, as supported in the specification, an oral dose of up to 250 mg/kg of 1-methylpropyl-2-imidazolyl disulfide is therapeutically effective. Additionally, Applicant teaches that injection of 1-methylpropyl-2-imidazolyl disulfide at 5, 10, and 15 mg/kg in *scid* mice significantly reduces tumor volumes. This provides support for Applicant's claims of 5-15 mg/kg (claims 31-32) and specifically claims of 5 mg/kg (claims 33-34), 10 mg/kg (claims 35-36) and 15 mg/kg (claims 37-38). The FDA has published a guideline on animal to human dosage conversion (Center for Drug Evaluation and Research, FDA). Using the FDA-recommended conversion method, a person of ordinary skill in the art would understand that this range is equivalent to 15-45 mg/m^2 in humans. Specifically, 5 mg/kg dosage in mice is equivalent to 15 mg/m^2 in human subjects, 10 mg/kg dosage in mice is equivalent to 30 mg/m^2 in human subjects, and 15 mg/kg dosage in mice is equivalent to 45 mg/m^2 in human subjects.

Moreover, Oblong fails to anticipate claims 9-10, 13-18, 21-22 and 25-40 because Oblong only teaches that the 2-imidazolyl disulfides of Oblong (including 1-methylpropyl 2-imidazolyl disulfide, also referred to as IV-2) inhibit the thioredoxin/thioredoxin reductase system (the "System"). Oblong, in fact, attributes this inhibition to the inhibition of thioredoxin reductase ("TR") (see Abstract of Oblong). Oblong does not describe inhibition of thioredoxin (as determined and claimed by Applicant); and Oblong's inhibition of the System is not indicative of pharmaceutical effectiveness. Moreover, Oblong reports essentially identical Ki and IC_{50} values for III-2, IV-2 and VII-2, and further describe these compounds as inhibitors of the System. Applicant unexpectedly found that select asymmetric disulfides behaved principally as inhibitors of thioredoxin rather than as substrates of TR. Despite their similarities in structure

and reported *in vitro* inhibitory activities, it was found that 1-methylpropyl-2-imidazolyl disulfide was, in fact, an inhibitor of thioredoxin, while structurally analogous compounds were functioning as substrates of TR. This is highlighted in Table 1 of Powis et al., where it teaches a difference of only two carbon atoms within the carbon chain (i.e. III-2 or VI-2 versus IV-2) renders a compound a substrate of TR instead of an inhibitor of thioredoxin, and dramatically impacts its suitability as a pharmaceutical composition. The fact that 1-methylpropyl-2-imidazolyl disulfide is a suitable pharmaceutical composition and neither III-2 or VI-2 are effective was first taught by Applicant.

Applicant is the first to disclose appropriate dosages of 2-imidazolyl disulfides, including 1-methylpropyl-2-imidazolyl disulfide, for injection and oral administration, and was the first to demonstrate the therapeutic effects of such dosages *in vivo*. For the foregoing reasons, Oblong fails to anticipate claims 7-40, and this rejection should be withdrawn.

35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 7-18 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Examiner has taken the position that the specification fails to provide support for "intravenous administration" as set forth in claims 7 and 8.

While respectfully disagreeing with the Examiner, Applicant has amended claims 7-8 to recite injection of 2-imidazolyl disulfide. Support for this amendment is found in paragraph [0215] of the specification. It is respectfully pointed out that in order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue, but rather the "disclosure must...convey with reasonable clarity to those skilled in the art that...[the inventor] was in possession of the invention." *See* MPEP 2163; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Applicant describes oral and intraperitoneal administration of 2-imidazolyl disulfide in paragraph [0215] of the specification. It is known to one of ordinary skill in the relevant art that intraperitoneal administration is done via an injection. Therefore, the specification more than adequately discloses and conveys to one ordinarily skilled in the art that the Applicant was in possession of the currently claimed invention (i.e., injection of 2-imidazolyl disulfide). As such, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,

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